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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

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12/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,298	GUITTON ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *October 12, 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/06;9/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of ketamine is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 2-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treatment of tinnitus" does not reasonably provide enablement for the "preventing tinnitus". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, and predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors**

have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method for preventing tinnitus induced by cochlear excitotoxicty in a human, the method comprising administering to a human a therapeutically effective amount of a pharmaceutical composition comprising an NMDA receptor antagonist (i.e. ketamine), effective to **prevent** NMDA receptor medicated aberrant activity of the auditory nerve in a human in need of such treatment. The nature of the invention is complex in that it encompasses the actual **prevention** of tinnitus such that the subject treated with above compounds does not contract tinnitus.

Breath of the Claims*:* The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass **prevention** of tinnitus in humans which has potentially many different causes (i.e. many different mutations or combination of mutations; medical disorders and drug-drug interaction). Each of which may or may not be addressed by the administration of the claimed compound.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compound to a subject in order to actually **prevent** tinnitus minimal. All of the guidance provided by the specification is directed towards treatment rather than prevention of tinnitus.

Working Examples: All of the working examples provided by the specification are directed toward the treatment rather than **prevention** of tinnitus.

State of the Art: While the state of the art is relatively high with regard to treatment of tinnitus the state of the art with regard to prevention of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to prevent development of tinnitus. The state of the art, Tabuchi et al. (2002) teach that the MK-801, the most potent NMDA receptor antagonist among ketamine and dextromethorphan, did not show any protective effect on cochlear ischemia reperfusion injury. (abstract). Tabuchi et al. concluded that NMDA antagonists do not have any protective effect on cochlear ischemia reperfusion injury, and this result is consistent with the morphological finding observed. (page 48, left-hand column middle paragraph). Therefore, instantly claimed **prevention** of such disorder is highly speculative.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual prevention of tinnitus in a human subject with the claimed compounds makes practicing the claimed invention unpredictable in terms of prevention of tinnitus.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine

whether or not the combination is effective for **prevention** of tinnitus. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard prevention of tinnitus with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding prevention of tinnitus with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of tinnitus in a subject by administration of one of the claimed compounds.

Therefore, a method for preventing tinnitus induced by cochlear excitotoxicty in a human, the method comprising administering to a human a therapeutically effective amount of a pharmaceutical composition comprising an NMDA receptor antagonist (i.e. ketamine), effective to **prevent** NMDA receptor medicated aberrant activity of the auditory nerve in a human in need of such treatment is not considered to be enabled by the instant specification.

4. Claims 1 and 4-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of tinnitus administering **specific NMDA receptor antagonist (i.e. ketamine)** does not reasonably provide enablement for the term **"an NMDA receptor antagonist"**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1 and 4-9 recite a method of treating tinnitus induced by cochlear excitotoxicty in a human, the method comprising administering to a human a therapeutically effective amount of **an NMDA receptor antagonist**. The guidance given by the specification as to how one would actually practice the invention of treating tinnitus with **any NMDA antagonist** is minimal. All of the guidance of the working examples are directed to administering **specific NMDA receptor antagonist (i.e. ketamine)**. The specification teaches how to treat tinnitus in a subject with specific NMDA receptor antagonist (i.e. ketamine), however, there are no working examples, prophetic or otherwise in the specification how to treat tinnitus with **any NMDA antagonists**. The state of the art with regard to determining the treatment of tinnitus with any NMDA antagonist in a subject is **not predictable**. The state of the art, Tabuchi et al. teach that MK-801, potent NMDA antagonist had no protective effect against ischemia-reperfusion injury of the cochlea but ketamine and dextromethorphan act as protective agent for the cochlea via other pathways. (abstract).

Given the complex nature of the invention, which involves administering any NMDA antagonist for treatment of tinnitus, the breadth of the claims which encompass

any NMDA antagonist (including MK 801), the complete lack of guidance from the specification regarding how to interpret the data generated by their methods toward understanding a treatment comprising administering any NMDA antagonist within a subject, complete lack of working examples, the uncertainty of whether the current state of the art regarding the use of such formulations would treat tinnitus. It would take undue, unpredictable experimentation to practice applicants' invention to employ any NMDA antagonist for the treatment of tinnitus. Therefore, a method of treating tinnitus induced by cochlear excitotoxicty in a human, the method comprising administering to a human a therapeutically effective amount of a pharmaceutical composition comprising **an NMDA antagonist** is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tabuchi et al. (2002) in view of Donovan (U.S.Patent No. 6,265,379 B1).

Tabuchi et al. teach that ketamine has protective effect against cochlear dysfunction induced by transient ischemia. (title). Tabuchi et al. teach that ketamine has protective effect against ischemia-reperfusion injury of the cochlea. (abstract). Tabuchi et al. teach that ketamine was administered intravenously. (page 45, left-hand column #1).

Tabuchi et al. do not expressly teach the treatment of tinnitus in human, site of local administration set forth in claims 5 and 6, and duration of cochlear excitotoxicty set forth in claims 7-9.

Donovan teaches that tinnitus, particularly inner ear tinnitus is due to cochlear nerve dysfunction. (column 2, lines 54-55). Donovan teaches local administration for the treatment of tinnitus includes injection. (column 5, lines 62-67).

It would have been obvious to one of ordinary skill in the art to employ ketamine for the treatment of tinnitus induced by cochlear excitotoxicty provoked by ischemia because Tabuchi et al. teach the protective effect of ketamine in cochlear injury/dysfunction due to ischemic-reperfusion and because tinnitus is a disorder of cochlea as taught by Donovan. One would have been motivated to employ ketamine for the treatment of tinnitus in order to achieve an expected benefit of protection against cochlear damage due to ischemic-reperfusion resulting tinnitus well known condition due to cochlear dysfunction by Donovan. Further, it would have been obvious to one of ordinary skill in the art to employ ketamine for the treatment of tinnitus in human because it is next logical step next to Tabuchi et al's successful ketamine treatment against protection of cochlear injury due to ischemic-reperfusion. One would have been motivated to employ ketamine in human suffering from tinnitus in order to achieve an expected benefit of protection of cochlea in vivo experimentation demonstrated by Tabuchi et al. With regard to determining the duration of the disease states set forth in claims 7-9 is obvious because it is a part of routine medical examination/diagnosis to find out the severity of the disease state and to determine optimum medical care that is necessary. Further, the affected loci within the inner ear membrane to be administered is obvious because tinnitus occurs in inner ear, therefore, one of ordinary skill in the art would directly to, in or to the vicinity of the inner ear in order to optimize the protection of

cochlear damaged by ischemic-reperfusion. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Kim
Primary Examiner
Art Unit 1617

Jmk
November 26, 2007